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Part IX

Department of Health, Education, and Welfare

National Institutes of Health

Recombinant DNA Research; Proposed Actions Under Guidelines; Recombinant DNA Advisory Committee; Meeting

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

Recombinant DNA Advisory Committee; Meeting

Pursuant to Pub. L. 92–463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee at the National Institutes of Health, Wilson Hall, Building 1, Bethesda, Maryland 20205, on March 6, 1980, from 9:00 a.m. to recess at approximately 6:00 p.m. and on March 7, 1980, from 8:30 a.m. to 5:00 p.m. This meeting will be open to the public on March 6 from 9:00 a.m. to recess at approximately 6:00 p.m., and on March 7, from 8:30 a.m. to 3:00 p.m., to discuss:

Amendment of Guidelines.
Containment practices appropriate for large-scale production.
Exceptions to prohibitions.
Exemptions for organisms that exchange genetic information.
Procedures for lowering characterized clones.
Review of large-scale experiments.
E. coli K–12 host-vector systems.
Host-vector systems other than *E. coli* K–12.
NIH risk-assessment plan.
Review of protocols for required containment levels.
Other matters requiring necessary action by the Committee.

Attendance by the public will be limited to space available.

In accordance with the provisions set forth in section 552b(c)(4), Title 5, U.S. Code and section 10(d) of Pub. L. 92–463, the meeting will be closed to the public on March 7 from 3:00 p.m. to 5:00 p.m. for the review, discussion and evaluation of proposal(s) from a commercial concern(s) for scale-up of recombinant DNA experiments. The proposal(s) and the discussions could reveal confidential trade secrets or commercial property such as patentable material.

Dr. William J. Gartland, Jr., Executive Secretary, Recombinant DNA Advisory Committee, National Institutes of Health, Building 31, Room 4A52, telephone 301–496–6051, will provide materials to be discussed at the meeting, rosters of committee members and substantive program information. A summary of the meeting will be available at a later date.

Dated: January 25, 1980.

Suzanne L. Fremeau,
Committee Management Officer, National Institutes of Health.

[FR Doc. 80–3040 Filed 1–30–80; 8:45 am]
BILLING CODE 4110–08–M

Recombinant DNA Research; Proposed Actions Under Guidelines

AGENCY: National Institutes of Health, PHS, DHEW.

ACTION: Notice of proposed actions under NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: This notice sets forth proposals for actions to be taken under the 1978 NIH Guidelines for Research Involving Recombinant DNA Molecules [Federal Register of December 22, 1978 (43 FR 60108)]. Interested parties are invited to submit comments concerning these proposals. After consideration of these proposals and comments by the NIH Recombinant DNA Advisory Committee (RAC) at its March 6–7, 1980, meeting, the Director of the National Institutes of Health will issue decision on these proposals in accord with the Guidelines.

DATE: Comments must be received by March 3, 1980.

ADDRESS: Written comments and recommendations should be submitted to the Director, Office of Recombinant DNA Activities, Building 31, Room 4A52, National Institutes of Health, Bethesda, Maryland 20205. All comments received in timely response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5:00 p.m.

FOR FURTHER INFORMATION CONTACT: Additional information can be obtained from Drs. Stanley Barban or Elizabeth Milewski, Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, Maryland 20205, (301) 496–6051.

SUPPLEMENTARY INFORMATION: The National Institutes of Health will consider the following changes and amendments under the Guidelines for Research Involving Recombinant DNA Molecules (43 FR 60108), as well as actions under these Guidelines.

1. *Amendment of Section IV–D–2–a.* As a comment on the Proposed Revised Guidelines for Research Involving Recombinant DNA Molecules published for comment in the Federal Register on November 30, 1979 (44 FR 69210), David Lester of Princeton, New Jersey, has proposed that Section IV–D–2–a, dealing with membership and procedures for the Institutional Biosafety Committee, be modified by adding as the penultimate sentence of IV–D–2–a the following:

"Such nonaffiliated members shall be appointed by the governing body of the community in which the institution is situated."

2. *Amendment of Section III–O of the Proposed Revised Guidelines.* Dr. Kent Wilcox of the Medical College of Wisconsin has suggested a clarification of the language of Section III–O, Classification of Experiments Using the *E. coli* K–12 Host-Vector Systems, of the proposed revised Guldelines published for comment in the Federal Register on November 30, 1979 (44 FR 69210). Section III–O is proposed to read, in part, as follows:

* * * For these experiments no Memorandum of Understanding and Agreement (MUA) as described in Section IV–D–1–c need be submitted, nor is any registration with NIH necessary. However, for these experiments, prior to their initiation, investigators must submit to their Institutional Biosafety Committee (IBC) a registration document that contains a description of (a) the source(s) of DNA, (b) the nature of the inserted DNA sequences, and (c) the hosts and vectors to be used. This registration document must be dated and signed by the investigator and filed only with the local IBC. The IBC shall review all such proposals but such review is not required prior to initiation of experiments. An exception, however, which does require prior review and approval by the IBC is any experiment in which there is a deliberate attempt to have the *E coli* K–12 efficiently express any gene coding for a eukaryotic protein * * *.

Dr. Wilcox suggests that the term "eukaryotic protein" is not well defined. He questions whether this term refers specifically to proteins encoded in the DNA of eukaryotic organisms and if so, whether animal viruses and viroids are considered to be eukaryotic organisms. Dr. Wilcox suggests that the last sentence of the above citation be modified to read as follows (modified text in italics):

* * * An exception, however, which does require prior review and approval by the IBC is any experiment in which there is a deliberate attempt to have the *E. coli* K–12 efficiently express *as a protein product the information carried in any gene derived either from a eukaryotic organism or from any virus or viroid which infects a eukaryotic organism* * * *.

3. *Amendment of Section III–O of the Proposed Revised Guidelines.* Dr. Stuart Levy of Tufts University School of Medicine has recommended an amendment to Section III–O of the Proposed Revised Guidelines (44 FR 69210). Dr. Levy notes that the plasmid studied in his risk-assessment studies was a nonconjugative poorly

mobilizable plasmid. He suggests that a distinction be made between nonconjugative plasmids and nonconjugative plasmids which are also poorly mobilizable; such an amendment would provide additional biological containment. The relevant portion of Section III–O of the Proposed Revised Guidelines which would be amended reads as follows:

* * * Other experiments using *E. coli* K–12 shall use P1 physical containment and, except as specified in the last paragraph of this section, an EK1 host-vector system (i.e., (a) the host shall not contain conjugation-proficient plasmids or generalized transducing phages, and (b) lambda or lambdoid bacteriophages or nonconjugative plasmids shall be used as vectors) * * *.

The amended section proposed by Dr. Levy would read as follows (amended text in italic):

* * * Other experiments using *E. coli* K–12 shall use P1 physical containment and, except as specified in the last paragraph of this section, an EK1 host-vector system (i.e., (a) the host shall not contain conjugation-proficient plasmids or generalized transducing phages, and (b) *lambda or lambdoid bacteriophages or nonconjugative poorly mobilizable (able to be mobilized at a frequency of less than 10^{-2} by a derepressed conjugative plasmid in the same cell) plasmids shall be used as vectors)* * * *.

4. *Request to Eliminate Section I–D–3 from the Guidelines.* In response to the proposed revised Guidelines published in the **Federal Register** on November 30, 1979 (44 FR 69210), Dr. Clarence Kado of the University of California, Davis, has asked the NIH to consider deleting from the Guidelines Section I–D–3 which reads as follows:

Deliberate creation by the use of recombinant DNA of a plant pathogen with increased virulence and host range beyond that which occurs by natural genetic exchange.[2A]

Dr. Kado explains his arguments for elimination of the prohibition in a letter to ORDA.

5. *Request to Include all Species of the Genus Erwinia in Appendix A, Sublist A.* In response to the proposed revised Guidelines published in the **Federal Register** on November 30, 1979 (44 FR 69210), Dr. Clarence Kado of the University of California, Davis, has requested that the NIH consider the inclusion of all *Erwinia* species in Sublist A, Appendix A. Currently, only one *Erwinia* species, *E. amylovora*, is included on the list. Dr. Kado suggests that consideration be given to all *Erwinia* species on the basis of an exchange of genetic material by natural means with *E. coli* and a 20% DNA–DNA homology of *E. coli* with *Erwinia* species.

6. *Classification of Plant Pathogens.* In response to the proposed revised Guidelines for Research Involving Recombinant DNA Molecules published in the **Federal Register** on November 30, 1979 (44 FR 69210), M. T. Goff, Animal and Plant Health Inspection Service, United States Department of Agriculture, has proposed that a classification of plant pathogens be included in the Guidelines. Philip D. Harriman, National Science Foundation, has also submitted a similar proposal. Messrs. Goff and Harriman request that a portion of the Report of a Workshop on Risk Assessment of Agricultural Pathogens, dealing with a hazard classification of plant pathogens, be included in the Guidelines. This Workshop was held on March 20–21, 1978, and the report appeared as Appendix G to the Environmental Impact Assessment which accompanied proposed revised Guidelines published for comment in the **Federal Register** of July 28, 1978 (43 FR 33042). Specifically, they request that the following classification be added to Appendix B of the Guidelines:

IV. Plant Pathogens

Class 1A Agents—Plant pathogens not in Class 1B.

Class 1B Agents—All organisms that are subject to quarantine restrictions for any of the following reasons:

(i) Plant pathogens not known to occur in the United States.

(ii) Plant pathogens that are not widely distributed throughout the ecological range of their hosts in the United States.

(iii) Plant pathogens subject to U.S. Federal or State eradication or suppression programs.

A USDA permit [2] is required to import or to move plant pathogens across State lines.

Footnote 2 of Appendix B of the proposed revised Guidelines reads as follows:

USDA permit also required for import and interstate transport.

It is proposed that this footnote be modified to read as follows in order to serve as a single footnote for both animal and plant pathogens:

[2] A USDA permit, required for import and interstate transport of pathogens, may be obtained form the Animal and Plant Health Inspection Service, USDA, Federal Building, Hyattsville, MD 20782.

7. *Containment Standards for Large-Scale Research and Production.* A Working Group on Large-Scale Research and Production prepared a draft set of physical containment standards for recombinant DNA research involving more than 10 liters of culture.

Comments on the draft standards were invited through January 10, 1980, in an announcement in the **Federal Register** of November 1, 1979 (44 FR 63074). Preliminary comments were reviewed by the RAC at its December 6–7, 1979 meeting. Comments will be taken into account by the Working Group in its preparation of a revised draft. Revised draft standards will be available from ORDA on February 1, 1980, and will be considered along with comments at the March 6–7, 1980 RAC meeting.

If eventually approved by the NIH Director, the substantive standards for large-scale work could be combined with the procedural standards recommended by the RAC at the September 1979 meeting or a subsequently revised version. The combined standards could then constitute a new Part VII of the NIH Guidelines.

8. *Proposal To Amend Portions of Section III–A–2–a, Viruses of Eukaryotes, of the Proposed Revised Guidelines.* In portions of Section III–A–2–a of the proposed revised Guidelines a level of biological containment requiring the use of "an HV1 host and a vector certified for use in an HV2 system" has been substituted for "an EK1 host and a vector certified for use in an EK2 system." This level of biological containment is abbreviated as "HV1CV" in Table III of the proposed revised Guidelines. At the December 6–7, 1979 meeting, a working group was appointed to review the appropriateness of this level of biological containment for the experiments described in this section of the Guidelines. The working group proposes that HV2 biological containment be required for these experiments. Therefore, the working group proposes that "an HV2 host-vector" be substituted for "an HV1 host and a vector for use in an HV2 system" in Sections III–A–2–a–(1)–(a)–(*2*)–(*c*), III–A–2–a–(1)–(a)–(*3*)–(*b*), III–A–2–a–(1)–(b)–(*1*)–(*b*), III–A–2–a–(1)–(b)–(*2*)–(*b*), III–A–2–a–(2)–(a)–(*1*)–(*b*), III–A–2–a–(2)–(a)–(*2*)–(*b*), and III–A–2–a–(2)–(c)–(*2*)–(*b*). In Table III, "HV2" would be substituted for "HV1CV."

9. *Request for Exemption Under Section I–E–4.* Dr. Francis Macrina of the Virginia Commonwealth University has proposed that *Streptococcus mutans* and *Streptococcus sanguis* be included under the exemption category of Section I–E–4 of the Guidelines on the basis that these bacteria have been shown to exchange chromosomal DNA by known physiological processes. These two organisms would then constitute a new Sublist of Appendix A.

10. *Request for Approval to Clone Exotoxin A Gene of Pseudomonas aeruginosa.* Dr. C. W. Shuster of Case Western Reserve University has requested the RAC to consider whether

the cloning of the exotoxin A gene of *Pseudomonas aeruginosa* in *E. coli* K–12 is permitted. Under exemption I–E–4, *P. aeruginosa* and genus *Escherichia* are listed in Appendix A, Sublist A. However, according to Section I–E, Exemptions:

It must be emphasized that the following exemptions (4) are not meant to apply to experiments described in the Sections I–D–1 to I–D–5 as being prohibited.

Section I–D–2 prohibits:

Deliberate formation of recombinant DNAs containing genes for the biosynthesis of toxins potent for vertebrates (2A) (e.g., botulinum, diphtheria toxins; venoms from insects, snakes, etc).

Dr. Shuster notes that exotoxin A and *P. aeruginosa* are safe under normal laboratory conditions. *P. aeruginosa* is an opportunistic pathogen and exotoxin A is only one of a series of virulence factor necessary to produce pathogenicity. This request was presented to the RAC at its December 6–7, 1979 meeting. At that time, the RAC felt that approval of the proposed experiments appeared to require an exception to a prohibition. Accordingly, the request is being published in the Federal Register for a 30 day comment period prior to being reconsidered by the RAC at its March 6–7, 1980 meeting.

11. *Request for Consideration of Appropriate Containment Levels.* Dr. Marvin Schwalb of New Jersey Medical School has requested that the RAC consider the containment levels appropriate to the return of *Schizophyllum commune* DNA cloned in *Saccharomyces cerevisiae* to *Schizophyllum commune.* In addition, Dr. Schwalb requests permission to clone the *S. cerevisiae* derived vector YR414/ura 3 and the *Saccharomyces* 2 plasmid containing yeast or *S. commune* sequences in *S. commune.*

2. *Request for Consideration of Appropriate Containment Levels.* Dr. Olen Yoder of Cornell University has asked the RAC to consider the appropriate containment level for the return of *Helminthosporanium maydis* DNA, which has been cloned in *Saccharomyces cerevisiae,* to the host of origin.

13. *Request to Lower Containment Conditions for Prokaryotic Cloning.* Dr. David Wilson of Cornell University has requested a lowering from P3 to P2 containment levels for experiments involving the cloning of the cellulase gene of *Sporocytophaga ep.* into a thermophilic *Bacillus.*

14. *Recombinant DNA Experiments Involving Foot-And-Mouth Disease Virus.* The RAC at its December 6–7, 1979 meeting recommended, and the Director, NIH, subsequently approved, the cloning of foot-and-mouth disease virus in *E. coli* K–12 at the Plum Island Animal Disease Center. The RAC further recommended, and the Director, NIH, subsequently approved, that prior to the shipment of any clones off of Plum Island, first a working group of the RAC and subsequently the full RAC would examine data arising from the foot-and-mouth disease virus recombinant DNA work on Plum Island.

If any such data are ready for presentation to the RAC, they will be considered at the March 6–7, 1980 meeting. The RAC analysis may include reexamination of the appropriate containment levels for experiments with any clones recommended to be shipped from Plum Island.

15. *Proposed EK2 Host-Vector Systems.* Dr. P. H. Pouwels of the Medisch Biologisch Laboratorium of Rijswijk, The Netherlands, has requested EK2 certification of several *trp* plasmids derived from plasmids pBR345 and pBR313. The *trp* vectors derived from pBR345 carry no antibiotic resistance genes. These plasmids would be used in conjunction with the host x1776 as an EK2 certified host-vector system.

16. *Revision of Section III–C–1–e of the Guidelines.* The proposed revised Guidelines (44 FR 69210), in Appendix C, cite a limited exemption, under Section I–E–5, for certain recombinant DNA experiments in tissue culture:

Under exemption I–E–5 of these Revised Guidelines are those recombinant DNA molecules that are propagated and maintained in cells in tissue culture and that are derived entirely from non-viral components (that is, no component is derived from a eukaryotic virus.).

This exemption was promulgated in the Federal Register of July 20, 1979 (44 FR 42914). In its original formulation (44 FR 22314), the exemption proposed to include recombinant DNA molecules that contain no more than one-fourth of the genome of a eukaryotic virus. At its December 6–7, 1979 meeting, Dr. Wallace Rowe submitted a document requesting that the RAC reconsider the question of allowing exemption for tissue culture experiments involving recombinant molecules containing no more than one-fourth of the genome of a virus. A working group was appointed to make recommendations for consideration at the March 6–7, 1980 meeting. It has been recommended that Sections III–C–1–e, III–C–1–e–(1), III–C–1–e–(1)–(a), and III–C–1–e–(1)–(b) of the Guidelines be changed and that a new Section III–C–1–e–(1)–(c) be added. Section III–C–1–e–(2) would remain unchanged. The proposed revised sections would read as follows:

III–C–1–e. *All Viral Vectors.*

III–C–1–e–(1). Other experiments involving eukaryotic virus vectors can be done as follows:

III–C–1–e–(1)–(a). Recombinant DNA molecules containing no more than two-thirds of the genome of any eukaryotic virus (all viruses from a single Family being considered identical) may be propagated and maintained in cells in tissue culture in the absence of helper virus using P1 containment. The DNA may contain fragments of the genomes of viruses from more than one Family but each fragment must be less than two-thirds of a genome. For such experiments, no MUA need be submitted but prior notice must be given to the IBC as described in Section III–0 of the Guidelines. The IBC should handle such registration documents as described in Section III–0.

"*III–C–1–e–(1)–(b).* Recombinants with less than two-thirds of the genome of any eukaryotic virus may be rescued with helper virus using P2 containment if wild type strains of the helper virus are not able to grow in human cells.

III–C–1–e–(1)–(c). Recombinants with less than two-thirds of the genome of any eukaryotic virus may be rescued with helper virus using P3 containment if wild-type strains of the helper virus are able to grow in human cells.

17. *Consideration of Appropriate Containment Levels.* Dr. Charles Jacobs of the University of Texas at Austin has requested permission from the RAC to clone *Wangiella dermatitidis* DNA in *Wangiella dermatitidis* using *Saccharomyuces/E. coli* hybrid plasmids as vectors. Dr. Jacobs requests that the RAC assess appropriate containment conditions.

Dated: January 23, 1980.

Donald S. Fredrickson, M.D.,

Director, National Institutes of Health.

[FR Doc. 80–3041 Filed 1–30–80; 8:45 am]

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